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Flexible approach for the asymmetric synthesis of (−)-hyacinthacine A1 and its 7a-epimer

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ABSTRACT

The diastereoselective nucleophilic addition of organic boronic ester to 3-hydroxy-2-substituted *N*-acyliminium ions **9** led to the formation of 2,5-*cis*-pyrrolidine **10**, from which a convenient synthesis of (−)-7a-*epi*-**1** was developed. In addition, an efficient asymmetric synthesis of (−)-hyacinthacine A1 **1** was achieved through the reduction/ring-opening process.

1. Introduction

Iminosugars (azasugars or iminocyclitols), the analogues of monosaccharides with nitrogen replacing the oxygen in the ring, are considered as mimics of sugars.[1] Most of these polyhydroxylated pyrrolizidine alkaloids (Fig. 1) and their structural motif proved to be a rich source of glycosidase or glycosyltransferase inhibitors. For example, australine **2** (IC_{50}=5.8 μM),[2] alexine **3** (IC_{50}=11 μM),[3] and hyacinthacine A2 **4a** (IC_{50}=8.6 μM)[4] are not only selective inhibitors of amyloglucosidase, but also demonstrate potential application as antiviral, anticancer, antidiabetic, and antiobesity drugs.[5] However, these iminosugars do not exhibit significant inhibition of β-glucosidases.[6] Among them, 3-(hydroxymethyl) pyrrolizidines, which were isolated from bluebells (*Hyacinthoides nonscripta*),[7a] grape hyacinths (*Muscari armeniacum*)[4] and from the bulbs of *Scilla peruviana*,[7b] *Scilla sibirica*,[7c] and *Scilla socialis*,[7d] are of particular interest. For example, (+)-hyacinthacine A1 **1**, isolated in 2000 from the bulbs of *M. armeniacum* (Hyacinthaceae) in less than 0.0005% yield,[4] displays good inhibitory activity against β-galactosidase from rat intestinal lactase (IC_{50}=4.4 μM) and is also a moderate inhibitor of both α-L-fucosidase from rat epididymis (IC_{50}=46 μM) and amyloglucosidase from *Aspergillus niger* (IC_{50}=25 μM). Due to the diverse biological activities in particular specific glycosidase inhibition, and the intriguing structure of (+)-hyacinthacine A1 **1** and their analogous, considerable efforts have been contributed to their synthesis and several enantioselective synthetic methods have been reported.[8]

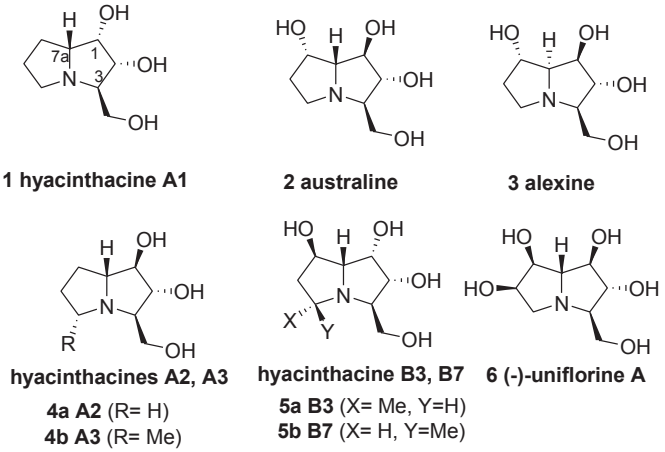

Fig. 1. The structures of several natural products.

The generation of four chiral centers in the pyrrolizidine skeleton is the most challenging part for the asymmetric synthesis of (+)-hyacinthacines. As a continuation of our interest in pursuing chiral building blocks and utilizing them in the synthesis of

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iminosugars,[9] ceramides,[10] piperidine,[11] and pyrrolidine[12] alkaloids, as well as divergent synthesis of depsipeptides,[13] we decided to develop an approach for the divergent synthesis of iminosugars using chiral lactam **7**, which was readily available from D-glutamic acid. Herein, we present this concise and flexible approach for the synthesis of (−)-hyacinthacine A1 **1** and its epimer 7a-*epi*-**1**.

The nucleophilic addition of allylic boronic ester to *N*-acyliminium ions for the formation of *cis* 5-substituted-4-hydroxy pyrrolidine-2-one or 6-substituted-5-hydroxypiperidin-2-ones was first reported by Batey in 1999.[14a] On the basis of this pioneered work, Pyne achieved an asymmetric method through diastereoselective borono-Mannich reaction of boronic acids and potassium trifluoroborate to cyclic *N*-acyliminium ions.[14b] Encouraged by these results, we envisioned that the 2,5-cis allylation could be realized through diastereoselective nucleophilic addition of *N*-acyliminium ions **9** with allyl borate or its corresponding ester, and the corresponding product could provide the right stereochemistry for C 7a in (−)-7a-*epi*-hyacinthacine A1. While the 2,5-trans allylation could be achieved by the nucleophilic addition of lactam **7** using Grignard reagents and subsequent diastereoselective reduction sequence.[15] Both strategies are outlined retrosynthetically in Fig. 2.

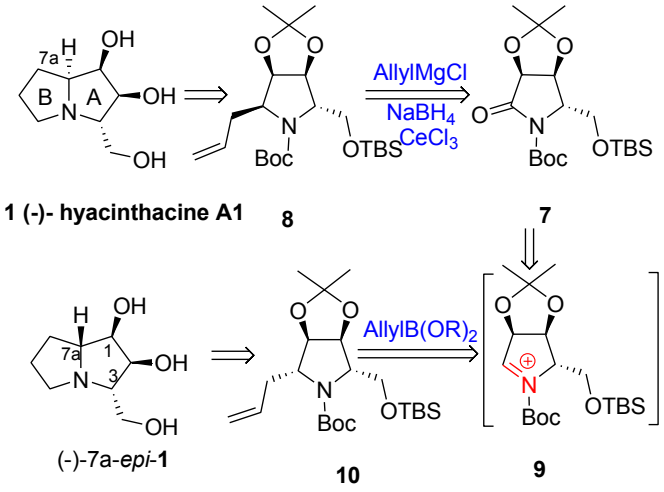
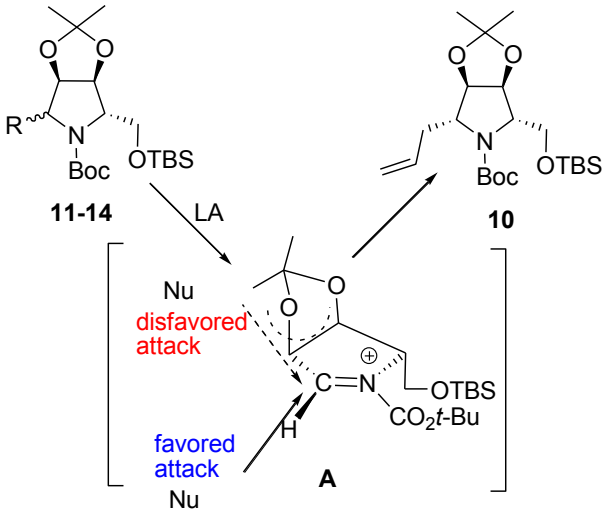


Fig. 2. Two different asymmetric allylations.

2. Results and discussion

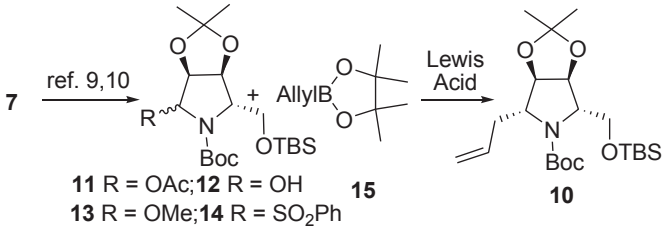
N,*O*-acetals **11**–**14** were prepared from lactam **7**, a derivative from D-glutamic acid in 73% overall yield.[9] Initially, the treatment of *N*,*O*-acetal **11** with allylboronic acid under Pyne's reaction conditions did not give any desired product **10**. But when the corresponding boronate, 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **15**, was used, compound **10** could be afforded in 36% yield with high diastereoselectivity (Table 1 entry 1). In order to improve the yield of **10**, various leaving groups of *N*,*O*-acetal were used, the yields did not get better (Table 1 entries 2–4). Fortunately, the aminal **12** (R=OH) turned out to be an excellent substrate for this allylation, and the yield of **10** could reach 61% when the reaction was conducted at −40 °C (Table 1, entry 5). Although several Lewis acids were screened, the results proved to be fruitless (Table 1, entries 6–9).

The stereochemistry of **10** was assigned as 2,5-cis-form, which can be rationalized by the Bürgi–Dunitz angle (BD angle).[16] The nucleophilic reagent attacked more stable conformation in the transition state **A** (Scheme 1) along 107° by the C=N bond.[17] Due to the influential steric effect of the acetal group, the attack toward downside should be more favorable than that of upside. Thus, nucleophilic addition to the transition state would produce



Scheme 1. The proposed mechanism of nucleophilic addition.

Table 1
The asymmetric alkylation of *N*,*O*-acetals **11**–**14**



Entry[a]	Lewis acid	*T*, °C	R	*Y*,[b] %	dr[c]
1	$BF_3{\cdot}Et_2O$	−78	OH	36	>99:1
2	$BF_3{\cdot}Et_2O$	−78 to −40	OAc	27	>99:1
3	$BF_3{\cdot}Et_2O$	−78 to −40	OMe	22	>99:1
4	$ZnCl_2$	−78 to −40	SO_2Ph	<5	—
5	$BF_3{\cdot}Et_2O$	−78 to −40	OH	61	>99:1
6	TMSOTf	−78 to −40	OH	43	>99:1
7	$TiCl_4$	−78 to −40	OH	17	>99:1
8	$ZnCl_2$	−78 to −40	OH	19	>99:1
9	$MgBr_2$	−78 to −40	OH	23	>99:1

[a] Reactions were performed with **11**, **12**, **13** or **14** (0.93 mmol), 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.27 mL, 1.39 mmol) in CH_2Cl_2 (20 mL) at −78 °C to −40 °C overnight.
[b] Isolated yield.
[c] dr was determined by ^1H NMR or HPLC.

the same facial to CH_2OTBS group eventually, that's a 2,5-cis chiral stereochemistry of **10**.

To further confirm the stereochemistry of C3 position, we decided to synthesize the (−)-7a-*epi*-hyacinthacine A1. Hydroboration of **10** with $BH_3{\cdot}SMe_2$ in tetrahydrofuran at room temperature, followed by oxidative hydrolysis with H_2O_2, gave primary alcohol **16** in 74% overall yield (Scheme 2).[18] Mesylation of compound **16** with methanesulfonyl chloride in the presence of triethylamine and subsequent treatment with TESOTf/2,6-lutidine could generate the cyclized product **17** in one-pot fashion in 75% overall yield. Finally, deprotection of compound **17** with MeOH/$(COCl)_2$ at room temperature for overnight gave the HCl salt of (−)-7a-*epi*-hyacinthacine A1 {$[\alpha]_D^{25}$ −38.8 (*c* 0.50, H_2O); lit.[8i] $[\alpha]_D^{25}$ +56.5 (*c* 0.12, H_2O)} in quantitative yield. The NMR spectroscopic data of synthetic 7a-*epi*-**1** were identical to the data of isolated (−)-7a-*epi*-hyacinthacine A1.[8i] The free base of (−)-7a-*epi*-hyacinthacine A1 was obtained, through Dowex 50WX8 ion-exchange resin, as a pale yellow syrup {$[\alpha]_D^{25}$ −45.3 (*c* 0.36, H_2O); lit.[8h] $[\alpha]_D^{25}$ +47 (*c* 0.65, H_2O)}. This further confirmed the stereochemistry